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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 08/934,367 | 09/19/1997 | PHILIP NEEDLEMAN | MON-103.0-(6 | 7395 |

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| EXAMINER |
|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 32 |

DATE MAILED: 09/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/934,367 | NEEDLEMAN ET AL. | |
| | Examiner | Art Unit | |
| | MINH-TAM DAVIS | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11 and 15-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 15-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *30* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **[04/21/03]** has been entered.

Accordingly, claims 1-11, 15-31 are examined in the instant application.

## INFORMATION DISCLOSURE STATEMENT

The references submitted in the information disclosure statement of paper No:30 on 04/21/03 have been carefully considered. It is noted that priority date of US 6,284,533 B1 has been determined to be the 102(e) date of 10/29/98. Therefore, US 6,284,533 B1 cannot be used as prior art rejection against the claims of the instant application, which has as priority date the filing date of 09/19/97.

## REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 22-23 remain rejected under 35 USC 112, second paragraph, pertaining to being indefinite, for reasons already of record in paper No:22.

Claims 22 and 23 are indefinite, because it is not clear in claims 22 and 23, what is meant by "polypeptides are each independently of a sequence".

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT**

Claims 2, 3, 5-11, 15-16, 23-27 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a process for increasing the concentration of HDL cholesterol in the blood of a mammal, for reasons already of record in paper No:22. Claims 1, 4, 22 are rejected for the same reasons already of record.

It is noted that claims 1, 4, 22 were inadvertently omitted from the rejection in previous Office action.

Applicant argues in paper No:21 that Table 1 represents a comparison of pre-immune sera and first-immune sera. Table 1 illustrates that even after a single inoculation, a measurable increase occur in HDL level. The claims are unrelated to table 1, and are drawn to repeated immunization. Applicant recites *In re Brana, In re Marzocchi, and In re Eltgroth*, stating that the PTO cannot make this rejection unless it has reason to doubt the objective truth of the statements in the written description. The Examiner has not presented evidence to refute the enablement of repeatly immunizing a mammal with an inoculum containing CETP immunogen, until the HDL cholesterol in the blood is increased to about 10 percent relative to the HDL cholesterol value prior to a first immunization.

The recitation of the case law *In re Brana, In re Marzocchi, and In re Eltgroth* is acknowledged.

Applicant's arguments set forth in paper No.21 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the claims encompass gene therapy in "human". Although the submitted reference by US 6,284,533 B1 (in IDS of paper No:30, submitted on 04/21/03) teaches successful vaccination of rabbits using a plasmid pCMV-CETP/TT encoding a) the rabbit C-terminal amino acids 481-496 of SEQ IS NO:2, wherein said amino acids are recognized by TP2, an antibody that inhibits CETP activity, b) a second epitope of the rabbit CETP comprising amino acids 350-368 of SEQ ID NO:2, and c) a tetanus toxoid sequence (Examples II-IV), in which rabbit 3 produces detectable antibody reactive with the rabbit CETP amino acids 479-496, and rabbits 3 and 6 have about 14% atherosclerotic lesions, much less than 44-40% atherosclerotic lesions in rabbits 2 and 5 that did not produce anti-CETP antibodies (Example III), the rabbit gene therapy is not an art accepted model for human gene therapy, because response in human to gene therapy is not the same as response to gene therapy in rabbits. For example, there are unpredictable serious adverse complications in human gene therapy, and recently gene therapy in human has been suspended (Marshall Eliot, 2002, Science, 298(5591): 34-5), and Salima, H et al, 2003, New England J Med, 348(3): 255-6).

Further, it is unpredictable that the HDL cholesterol value in the blood of a mammal would be increased by "about 10 percent or more" relative to the HDL

cholesterol value prior to immunization with recombinant human or rabbit CETP, because the 10 percent value is based on the data in Table 1, wherein it seems that said 10 percent difference is not reliable because of variation within samples, rather than a significant difference in HDL between the control and the animals immunized with recombinant human CETP or with C-terminal rabbit CETP conjugated to thyroglobulin.

It is noted that although the submitted reference by US 6,284,533 B1 (in IDS of paper No:30, submitted on 04/21/03) teaches successful vaccination of rabbits using a plasmid pCMV-CETP/TT encoding a) the rabbit C-terminal amino acids 481-496 of SEQ IS NO:2, wherein said amino acids are recognized by TP2, an antibody that inhibits CETP activity, b) a second epitope of the rabbit CETP comprising amino acids 350-368 of SEQ ID NO:2, and c) a tetanus toxoid sequence (Examples II-IV), in which rabbit 3 produces detectable antibody reactive with the rabbit CETP amino acids 479-496, and rabbits 3 and 6 have about 14% atherosclerotic lesions, much less than 44-40% atherosclerotic lesions in rabbits 2 and 5 that did not produce anti-CETP antibodies (Example III), US 6,284533 does not teach quantitation of the HDL cholesterol value prior to and after immunization. Further, although the absolute level of HDL cholesterol is generally correlated with decrease in susceptibility to cardiovascular disease such as atherosclerotic lesions (US 6,284,533 B1, column 2, second paragragph), one cannot predict the exact percentages of change of the level of HDL in rabbits or in a mammal that would be required to produce about 14% atherosclerotic lesions, as compared to

44-40% atherosclerotic lesions, because one would expect that changes in the level of atherosclerotic lesions depend on several factors, and not just only on the level of HDL.

Moreover, although the submitted reference by US 6,410022 B1 (in IDS of paper No:30, submitted on 04/21/03) teaches that vaccination of rabbits with complex comprising a polypeptide sequence comprising the CETP human amino acids 461 to 467 and a tetanus toxoid sequence produce a 2 to 5 fold increase in the HDL-C concentration (Example 4), the level of responses of an animal to DNA vaccine is not expected to be the same as its level of responses to a corresponding peptide vaccine, because there are several factors that are different between a DNA and a peptide vaccine, such as the efficiency of the vector containing the desired DNA, which is not a consideration for a peptide vaccine.

Further, US 6,284533 ( in IDS of paper No:30, submitted on 04/21/03 )only contemplates the use of similar plasmid for the corresponding human CETP fragment, linked in the same reading frame to a tetanus toxoid or diphtheria toxin sequence, with or without intervening linker sequence (Example IV). Therefore, one cannot predict which percentage of increase in the level of HDL, and which percentage of decrease in the level of atherosclerotic lesions are found in human or any mammal, because different animals have different reactions with drugs.

Further, it is unpredictable that using full length CETP would increase the concentration of HDL cholesterol, because full length CETP could exhibit CE and/or TG transfer activity and thereby increase the overall CETP activity in the vaccinated

individual (US 6,284533, column 12, last paragraph). and thus negating the action of antibodies against CETP.

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE OF ENABLEMENT**

Claims 1-11, 16, 23-27 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a process of increasing the concentration of HDL using any DNA fragment of CETP, or full length sequence of CETP, for reasons already of record in paper No:22. Claims 17-22, 29-31 are rejected for the same reasons of record.

Applicant argues in paper No:21 that the specification gives operative examples of sequences known to be both antigenic and antagonistic to CETP. In order to fall within the scope of claims 1-11, and 16-31, as amended, the CETP immunogen must both raise antibodies and increase HDL-cholesterol. Because those skilled in the art would appreciate that certain CETP amino acid residue sequences raised antibodies and are antagonistic with respect to CETP biological activity, Applicant is entitled to the full scope of these claims.

Applicant's arguments set forth in paper No.21 have been considered but are not deemed to be persuasive for the following reasons:

Rejection remains, because not any fragment of a protein is involved in its activity, and it is unpredictable that any 10 to 30 residues of an immunogenic sequence of CETP, or SEQ ID Nos: 2, 3, 6-9, 11-13, 32-33, 35-37 are in a region that is involved in the biological activity of CETP, such that antibodies specific for these claimed

sequences would inhibit the biological activity of CETP. Further, it is unpredictable whether the claimed sequences are exposed on the surface of CETP such that antibodies against these claimed sequences could bind to CETP via the claimed sequences.

Further, it is unpredictable that using full length CETP would increase the concentration of HDL cholesterol, because full length CETP could exhibit CE and/or TG transfer activity and thereby increase the overall CETP activity in the vaccinated individual (US 6,284533, column 12, last paragraph). and thus negating the action of antibodies against CETP.

Moreover, claims 22

**REJECTION UNDER 35 USC 102 (b)**

Claim 29 remains rejected under 35 USC 102(b), pertaining to anticipation by Jeong et al, for reasons already of record in paper No:22.

Applicant asserts in paper No:21 that claim 29 has been amended to include a limitation of a CETP amino acid residue sequence of about 10 to 30 residues . Jeong does not teach a CETP amino acid residue sequence of about 10 to 30 residues.

Applicant's arguments set forth in paper No.21 have been considered but are not deemed to be persuasive for the following reasons:

The DNA molecule encoding a the claimed complex comprising a CETP amino acid residue sequence of "about 10 to 30 residues" still reads on the DNA sequence comprising the 31 amino acid sequence taught by Jeong et al.

**REJECTION UNDER 35 USC 103**

Claims 29, 30 remain rejected under 35 USC 103, pertaining to being obvious over Jeong et al, in view of US 5,650298 for reasons already of record in paper No:22.

Applicant asserts in paper No:21 that claim 29 has been amended to include a limitation of a "CETP amino acid residue sequence of about 10 to 30 residues" and that. Jeong does not teach a CETP amino acid residue sequence of about 10 to 30 residues. Applicant further asserts that the secondary reference does not suggest combining with or modifying Jeong in such as way as to make claims 29 and 30 obvious.

Applicant's arguments set forth in paper No.21 have been considered but are not deemed to be persuasive for the following reasons:

A CETP amino acid residue sequence of "about 10 to 30 residues" of claim 29 still reads on the 31 amino acid sequence taught by Jeong et al.

Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Thus, it would have been obvious to replace the promoter taught by Jeong et al with any other promoter, because they all would produce the claimed protein.

2. Rejection under 35 USC 103 claims 1, 2, and 22 pertaining to obviousness by Jeong et al, in view of Felgner et al, further in view of Silversides et al remains for reasons already of record in paper No.18.

Rejection remains because Applicant has not answered to the rejection in paper No: 21.

**REJECTION UNDER 35 USC 103, NEW REJECTION**

Claims 17-21, 28-31 are rejected under 35 USC 103, as being obvious over US 6, 410,022 B1, in IDS of paper No:30, submitted on 04/21/03, in view of Drayna, D et al, 1987, Nature, 327: 632-634, Nagashima M et al, Journal of lipid research (UNITED STATES) Dec 1988, 29 (12): 1643-9, Eisel U et al, EMBO journal (ENGLAND) Oct 1986, 5 (10) p2495-502, Baier G et al, BioTechniques (UNITED STATES) Jul 1994, 17 (1) p94, 96, 98-9, and Johnstone et al (Immunochemistry in Practice, 2nd Ed., 1987, Blackwell Scientific Publications, Oxford, pages 49-50).

Claims 17-21, 28-31 are drawn to an inoculum, comprising a pharmaceutically acceptable vehicle containing a recombinant DNA, comprising a DNA sequence that contains (i) a sequence encoding a CETP immunogen, or a human CETP immunogen, linked to (ii) a promoter sequence, said CETP immunogen comprising an antigenic carrier to which is covalently bonded one or more immunogenic polypeptides comprising a CETP amino acid sequence of about 10 to about 30 residues. The concentration of said DNA encoding said CETP immunogen is about 0.05 ug/ml to about 20 mg/ml (claim 18). Said DNA is complexed with liposomes (claim 21). Said

DNA is contained in a pharmaceutically acceptable vehicle,which is phosphate buffer saline or isotonic sucrose. Said one or more immunogenic polypeptide are selected from the group consisting of SEQ ID NOs: 4, 10, 29 or 50 (claims 28, 31). Said promoter sequence is a cytomegalovirus immediate-early promoter sequence (CMV) (claim 30).

It is noted that SEQ ID NOs:29 and 50 represent the 26 C-terminal amino acids of human and rabbit CETP, respectively.

It is further noted that SEQ ID NOs: 4 and 10 represent the last 22 C-terminal amino acids of SEQ ID NOs: 50 and 29 respectively (see sequence listing of SEQ ID Nos: 4, 10, 29 and 50).

In addition, it is noted that the claims 17-21, 28-31 recite the claimed recombinant DNA, formulated as an inoculum. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. The claims 17-21, 28-31 read on the ingredient per se, which is a recombinant DNA, comprising a DNA sequence that contains (i) a sequence encoding a CETP immunogen, or a human CETP immunogen, linked to (ii) a promoter sequence said CETP immunogen comprising an antigenic carrier to which is covalently bonded one or more CETP immunogenic polypeptides.

US 6, 410,022 B1 teaches vaccination of rabbits using a complex comprising a B cell epitope portion comprising a carboxyl terminal region or C-terminal 26 amino acids of human CETP, and a universal tetanus toxoid helper T cell epitope (column 7, item B and Example I). US 6, 410,022 B1 teaches that an example of said complex comprises a) the rabbit C-terminal amino acids 461-476 of human CETP, wherein said amino acids

are recognized by TP2, an antibody that inhibits CETP activity, and b) a tetanus toxoid sequence to elicit an immune response against endogenous rabbit CETP (Examples I-II). US 6, 410,022 B1 teaches that said complex shows a 2-5 fold increase in HDL concentration in treated rabbits (Example 4). US 6, 410,022 B1 teaches that injection of said complex into transgenic mice expressing human CETP produce anti-CETP antibody that competes with Mab TP2 for binding to recombinant CETP (Example V). US 6, 410,022 B1 also teaches covalent linking between a helper T cell epitope and CETP fragment (column 10, second paragraph). US 6, 410,022 B1 teaches that decreased susceptibility to cardiovascular disease, such as atherosclerosis, is generally correlated with increased absolute level of circulating HDL (column 1, last paragraph)

US 6, 410,022 B1 does not teach a recombinant DNA, comprising a DNA sequence that contains (i) a sequence encoding a CETP immunogen, or a human CETP immunogen, linked to (ii) a promoter sequence, said CETP immunogen comprising an antigenic carrier to which is covalently bonded one or more immunogenic polypeptides comprising a CETP amino acid sequence of about 10 to about 30 residues. US 6, 410,022 B1 does not teach that the concentration of said DNA encoding said CETP immunogen is about 0.05 ug/ml to about 20 mg/ml and that said DNA is complexed with liposomes, and contained in a pharmaceutically acceptable vehicle which is phosphate buffer saline or isotonic sucrose. US 6, 410,022 B1 does not teach that said one or more immunogenic polypeptide are selected from the group consisting of SEQ ID NOs: 4, 10, 29 or 50 (claims 28, 31). US 6, 410,022 B1 does not teach that

said promoter sequence is a cytomegalovirus immediate-early promoter sequence (CMV).

Drayna, D et al teach cDNA cloning of human CETP.

Nagashima M et al teach cDNA cloning of rabbit CETP.

Eisel U et al teach cDNA cloning of tetanus toxin.

Baier G et al teach an improved mammalian expressiion vector having CMV promoter for efficient expression of recombinant gene product.

Johnstone et al teach that it was common practice in the art at the time of applicant's invention to formulate compositions of antibodies and PBS, which is considered in the art to be an acceptable carrier for storage of proteins and DNA

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made 1) to make a DNA sequence encoding a complex taught by US 6, 410,022 B1, comprising rabbit or human CETP C-terminal amino acids conjugated to a carrier such as tetanus toxin taught by US 6, 410,022 B1, using the known cDNA sequences of rabbit or human CETP taught by Nagashima M et al and Drayna, D et al, respectively, and the known cDNA sequence of tetanus toxin taught by Eisel U et al, and 2) to insert said DNA sequence in a mammalian expression vector having CMV promoter taught by Baier G et al for the following reasons: 1) Expressing recombinant gene products in a mammalian expression vector having CMV promoter as taught by Baier G et al is common in the art, 2) The encoded C-terminal amino acids of CETP of the complex would produce antibody specific for CETP and increase the HDL

concentration, as taught by US 6, 410,022 B1, which is known in the art to be correlated with susceptibility to cardiovascular diseases.

It would have been obvious to complex said DNA sequence with liposomes, because liposomes are well known in the art for use in delivery of therapeutic agents.

Further it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include a carrier in the composition because Johnstone and Thorpe teach that it was common practice in the art at the time of applicant's invention to formulate compositions of antibodies and PBS, which is considered in the art to be an acceptable carrier for storage of proteins and DNA. One of ordinary skill would have been motivated to do so in order to develop compositions suitable for storage. Finally, it has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See *In re Rosicky*, 125 USPQ 341 (CCPA 1960).

With regards to the concentration of the claimed DNA encoding said CETP immunogen of about 0.05 ug/ml to about 20 mg/ml recited in claim 18, to determine optimum concentration of reactants is within the level of ordinary skill in the art. See In re Kronig, 190 USPQ 425.

One of ordinary skill in the art would have been motivated to make a DNA sequence contains (i) a sequence encoding a CETP immunogen, or a human CETP immunogen, linked to (ii) a promoter sequence, said CETP immunogen comprising an antigenic carrier to which is covalently bonded one or more immunogenic polypeptides

comprising a CETP amino acid sequence with a reasonably expectation of success in making said DNA sequence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY

MINH TAM DAVIS

August 7, 2003